

## CLAIMS

What is claimed is:

1. A transgenic fish whose genome has stably integrated therein an oncogene operably linked to a promoter.
- 5 2. The transgenic fish of claim 1, wherein the promoter is an organ- or a tissue-specific promoter.
3. The transgenic fish of claim 2, wherein the tissue-specific promoter is selected from the group consisting of *Keratin-8*, *Islet-1*, *PDX-1*, *insulin*, *GFAP*, *MYO-D*, *alpha-actin*, *tyrosine hydroxylase*, *MPO*, and *PU.1*  
10 promoters.
4. The transgenic fish of claim 2, wherein the promoter is a lymphoid-specific promoter.
5. The transgenic fish of claim 4, wherein the promoter is a B-cell- or T-cell-specific promoter.
- 15 6. The transgenic fish of claim 4, wherein the lymphoid-specific promoter is selected from the group consisting of *RAG1*, *RAG2*, and *CD2* promoters.
7. The transgenic fish of claim 4, wherein the promoter is a T-cell progenitor-specific promoter.
8. The transgenic fish of claim 1, wherein the promoter is a *RAG2* promoter.
- 20 9. The transgenic fish of claim 1, wherein the oncogene is selected from the group consisting of *MYC*, *CYCLIN D1*, *FOS*, *JUN*, *MYB*, *BCL2*, *HOX11*, *HOX11L2*, *LYL1*, *TAL1/SCL*, *LMO1*, *LMO2*, *MYCN*, *MDM2*, *CDK4*, *GLI1*, *IGF2*, activated *RAS*, activated *EGFR*, mutated *FLT3-ITD*, mutated and activated versions of *TP53*, *PAX3*, *PAX7*, *BCR/ABL*, *HER2/NEU*,

*FLT3R, NPM-ALK, SRC, RAS, ABL, TAN1, PTC, B-RAF, PML-RAR $\alpha$ , and E2A-PBX1.*

10. The transgenic fish of claim 9, wherein the oncogene is a mammalian homologue of the oncogene.
- 5 11. The transgenic fish of claim 1, wherein the oncogene is a T-cell oncogene.
12. The transgenic fish of claim 11, wherein the T-cell oncogene is a member of a gene family selected from the group consisting of the *MYC*, *TAL1/SCL*, *TAL2*, *LYL1*, *LMO1*, *LMO2*, *HOX11*, *HOX11L2*, *TAN1*, and *LYL1* gene families.
- 10 13. The transgenic fish of claim 12, wherein the oncogene is a mammalian homologue of the T-cell oncogene.
14. The transgenic fish of claim 1, wherein the oncogene is a B-cell oncogene.
15. The transgenic fish of claim 14, wherein the B-cell oncogene is a member of a gene family selected from the group consisting of the *MYC*, *E2A-PBX1*, *E2A-HLF*, *TEL-AML1*, *BCL6*, *BCL3*, *LYT10*, *MLL*, *HOX*, and *PAX5* gene families.
- 15 16. The transgenic fish of claim 15, wherein the oncogene is a mammalian homologue of the B-cell oncogene.
17. The transgenic fish of claim 1, wherein the oncogene is *cMYC* or *BCL2*.
- 20 18. The transgenic fish of claim 1, wherein the oncogene is substantially similar to *cMYC* or *BCL2*.
19. The transgenic fish of claim 1, wherein the oncogene is fused to a reporter gene.

20. The transgenic fish of claim 19, wherein the reporter gene is selected from the group consisting of luciferase,  $\beta$ -galactosidase, chloramphenicol, acytransferase,  $\beta$ -glucuronidase, and alkaline phosphatase.
- 5 21. The transgenic fish of claim 19, wherein the reporter gene is a fluorescent protein gene.
22. The transgenic fish of claim 21, wherein the fluorescent protein gene is selected from the group consisting of *GFP*, *RFP*, *BFP*, *YFP*, and *dsRED2*.
23. The transgenic fish of claim 22, wherein the fluorescent protein gene is *GFP*.
- 10 24. A transgenic fish whose genome has stably integrated therein a *cMYC* oncogene operably linked to a *RAG2* promoter, wherein the *cMYC* oncogene is fused to a green fluorescent protein gene.
25. A transgenic fish whose genome has stably integrated therein a ubiquitous gene promoter, a reporter gene comprising a strong transcription stop-site, and an oncogene, wherein the reporter gene is flanked by site-specific recombinase recognition sites.
- 15 26. The transgenic fish of claim 25, wherein the site-specific recombinase recognition sites are selected from the group consisting of Flox, Lox, and FRT.
- 20 27. The transgenic fish of claim 25, wherein the ubiquitous gene promoter is *CMV*, *EF1-alpha*, or *beta-actin*.
28. The transgenic fish of claim 25, wherein the reporter gene is selected from the group consisting of luciferase,  $\beta$ -galactosidase, chloramphenicol, acytransferase,  $\beta$ -glucuronidase, and alkaline phosphatase.
- 25 29. The transgenic fish of claim 25, wherein the reporter gene is a fluorescent protein gene.

30. The transgenic fish of claim 29, wherein the fluorescent protein gene is selected from the group consisting of *GFP*, *RFP*, *BFP*, *YFP*, and *dsRED2*.
31. The transgenic fish of claim 1, wherein the oncogene induces oncogene-mediated cancer progression, and wherein the cancer is selected from the group consisting of non-Hodgkin's lymphoma, high-grade astrocytoma, rhabdomyosarcoma, neuroblastoma, neuroendocrine carcinoma, pancreatic carcinoma, ovarian carcinoma, testicular carcinoma, stomach cancer, colon cancer, renal cancer, melanoma, acute myeloid leukemia, chronic myeloid leukemia, and *cMYC*-induced T-cell acute lymphoblastic leukemia.
32. The transgenic fish of claim 1, wherein the oncogene is fused to *ER*.
33. The transgenic fish of claim 32, wherein the *ER* is tamoxifen-sensitive *ER* (*ER<sup>Tm</sup>*).
34. The transgenic fish of claim 1, wherein the transgenic fish is a transgenic zebrafish.
35. A transgenic zebrafish whose genome has stably-integrated therein a mouse *cMYC* oncogene operably linked to a zebrafish *RAG2* promoter.
36. A method of screening drugs or agents that modulate oncogene-mediated neoplastic or hyperplastic transformation, comprising:
- contacting or otherwise exposing a transgenic fish to a test drug or agent, wherein the transgenic fish has a genome that has stably integrated therein an oncogene operably linked to a promoter;
- determining if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation; and

classifying the test drug or agent as a drug or agent that modulates oncogene-mediated neoplastic or hyperplastic transformation if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation.

- 5     37.     The method of claim 36, wherein the promoter is an organ- or a tissue-specific promoter.
38.     The method of claim 37, wherein the tissue-specific promoter is selected from the group consisting of *Keratin-8*, *Islet-1*, *PDX-1*, *insulin*, *GFAP*, *MYO-D*, *alpha-actin*, *tyrosine hydroxylase*, *MPO*, and *PU.1* promoters.
- 10    39.     The method of claim 37, wherein the promoter is a lymphoid-specific promoter.
40.     The method of claim 39, wherein the promoter is a B-cell- or T-cell-specific promoter.
41.     The method of claim 39, wherein the lymphoid-specific promoter is  
15       selected from the group consisting of *RAG1*, *RAG2*, and *CD2* promoters.
42.     The method of claim 39, wherein the promoter is a T-cell progenitor-specific promoter.
43.     The method of claim 36, wherein the promoter is a *RAG2* promoter.
44.     The method of claim 36, wherein the oncogene is selected from the group  
20       consisting of *MYC*, *CYCLIN D1*, *FOS*, *JUN*, *MYB*, *BCL2*, *HOX11*, *HOX11L2*, *LYL1*, *TAL1/SCL*, *LMO1*, *LMO2*, *MYCN*, *MDM2*, *CDK4*, *GLI1*, *IGF2*, activated *RAS*, activated *EGFR*, mutated *FLT3-ITD*, mutated and activated versions of *TP53*, *PAX3*, *PAX7*, *BCR/ABL*, *HER2/NEU*, *FLT3R*, *NPM-ALK*, *SRC*, *RAS*, *ABL*, *TAN1*, *PTC*, *B-RAF*, *PML-RAR $\alpha$* , and  
25       *E2A-PBX1*.

45. The method of claim 44, wherein the oncogene is a mammalian homologue of the oncogene.
46. The method of claim 36, wherein the oncogene is a T-cell oncogene.
47. The method of claim 46, wherein the T-cell oncogene is a member of a gene family selected from the group consisting of the *MYC*, *TAL1/SCL*, *TAL2*, *LYL1*, *LMO1*, *LMO2*, *HOX11*, *HOX11L2*, *TAN1*, and *LYL1* gene families.
48. The method of claim 47, wherein the oncogene is a mammalian homologue of the T-cell oncogene.
49. The method of claim 36, wherein the oncogene is a B-cell oncogene.
50. The method of claim 49, wherein the B-cell oncogene is a member of a gene family selected from the group consisting of the *MYC*, *E2A-PBX1*, *E2A-HLF*, *TEL-AML1*, *BCL6*, *BCL3*, *LYT10*, *MLL*, *HOX*, and *PAX5* gene families.
51. The method of claim 50, wherein the oncogene is a mammalian homologue of the B-cell oncogene.
52. The method of claim 36, wherein the oncogene is *cMYC* or *BCL2*.
53. The method of claim 36, wherein the oncogene is substantially similar to *cMYC* or *BCL2*.
54. The method of claim 36, wherein the oncogene is fused to a reporter gene.
55. The method of claim 54, wherein the reporter gene is selected from the group consisting of luciferase,  $\beta$ -galactosidase, chloramphenicol, acytransferase,  $\beta$ -glucuronidase, and alkaline phosphatase.

56. The method of claim 55, wherein the reporter gene is a fluorescent protein gene.
57. The method of claim 56, wherein the fluorescent protein gene is selected from the group consisting of *GFP*, *RFP*, *BFP*, *YFP*, and *dsRED2*.
- 5 58. The method of claim 57, wherein the fluorescent protein gene is *GFP*.
59. The method of claim 36, wherein the oncogene is *cMYC* and the promoter is *RAG2*, and wherein the *cMYC* oncogene is fused to a green fluorescent protein gene.
- 10 60. A method of screening drugs or agents that modulate oncogene-mediated neoplastic or hyperplastic transformation, comprising:
- contacting or otherwise exposing a transgenic fish to a test drug or agent, wherein the transgenic fish has a genome that has stably integrated therein a ubiquitous gene promoter, a reporter gene comprising a strong transcription stop-site, and an oncogene, and wherein the reporter gene is flanked by site-specific recombinase recognition sites;
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- determining if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation; and
- classifying the test drug or agent that modulates oncogene-mediated neoplastic or hyperplastic transformation if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation.
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61. The method of claim 60, wherein the site-specific recombinase recognition sites are selected from the group consisting of Flox, Lox, and FRT.
- 25 62. The method of claim 61, further comprising administering a polynucleotide encoding *CRE* or *Flip*.

63. The method of claim 60, wherein the ubiquitous gene promoter is *CMV*, *EF1-alpha*, or *beta-actin*.
64. The method of claim 60, wherein the reporter gene is selected from the group consisting of luciferase,  $\beta$ -galactosidase, chloramphenicol, acytransferase,  $\beta$ -glucuronidase, and alkaline phosphatase.
65. The method of claim 60, wherein the reporter gene is a fluorescent protein gene.
66. The method of claim 65, wherein the fluorescent protein gene is selected from the group consisting of *GFP*, *RFP*, *BFP*, *YFP*, and *dsRED2*.
67. The method of claim 36, wherein the oncogene induces oncogene-mediated cancer progression, and wherein the cancer is selected from the group consisting of non-Hodgkin's lymphoma, high-grade astrocytoma, rhabdomyosarcoma, neuroblastoma, neuorendocrine carcinoma, pancreatic carcinoma, ovarian carcinoma, testicular carcinoma, stomach cancer, colon cancer, renal cancer melanoma, acute myeloid leukemia, chronic myeloid leukemia, and *cMYC*-induced T-cell acute lymphoblastic leukemia.
68. The method of claim 36, further comprising measuring the rate of onset of tumor formation resulting from oncogene-mediated neoplastic or hyperplastic transformation.
69. The method of claim 36, further comprising measuring the amount or size of tumors resulting from oncogene-mediated neoplastic or hyperplastic transformation.
70. The method of claim 36, wherein the test drug or agent is antisense DNA, antisense RNA, or small interfering RNA.



71. The method of claim 36, wherein the transgenic fish is a transgenic fish embryo.
72. The method of claim 36, wherein the transgenic fish is a transgenic zebrafish.
- 5 73. The method of claim 71, wherein the transgenic fish embryo is a transgenic zebrafish embryo.
74. A method of screening drugs or agents that modulate oncogene-mediated neoplastic or hyperplastic transformation, comprising:
- 10           contacting or otherwise exposing a transgenic zebrafish to a test drug or agent, wherein the transgenic zebrafish genome has stably-integrated therein a mouse *cMYC* oncogene operably linked to a zebrafish *RAG2* promoter;
- determining if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation; and
- 15           classifying the test drug or agent that modulates oncogene-mediated neoplastic or hyperplastic transformation if the test drug or agent modulates oncogene-mediated neoplastic or hyperplastic transformation.